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N-Halogeno compounds. Part 15. Synthesis of *N*-fluoroquinuclidinium salts via direct fluorination of quinuclidine–Lewis acid adducts, and a comparison of their "F^+" transfer capabilities [1]

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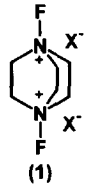
Abstract

Fluorine smoothly attacks quinuclidine–trifluoroborane, quinuclidine–pentafluorophosphorane, and quinuclidine–sulfur trioxide in acetonitrile at −35 °C to give the corresponding *N*-fluoroquinuclidinium salts NFQ^+X^- ($X^- = BF_4^-$, PF_6^-, and FSO_3^- respectively; Q = quinuclidine). Like its tetrafluoroborate analogue ($NFQ^+BF_4^-$), the hexafluorophosphate $NFQ^+PF_6^-$ can also be prepared by direct fluorination of quinuclidine in the presence of the appropriate sodium salt ($NaPF_6$). An alternative route to the tetrafluoroborate involves treatment of NFQ^+F^- with boron trifluoride. A comparative study of site-specific electrophilic fluorination of methoxybenzene [→ 1-fluoro-2- and 4-methoxybenzene], 2-hydroxynaphthalene (→ 1-fluoro-2-hydroxynaphthalene and 1,1-difluoro-2-oxo-1,2-dihydronaphthalene), 2-nitropropan-2-yl-lithium (→ 2-fluoro-2-nitropropane) and diethyl sodio(phenyl)malonate [→ diethyl fluoro(phenyl)malonate] with all of the NFQ^+X^- salts mentioned above, plus the triflate ($X^- = CF_3SO_3^-$), revealed that the hexafluorophosphate and triflate are the most easily-handled and effective reagents.

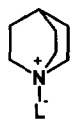
Keywords: *N*-halogeno compounds; *N*-fluoroquinuclidinium salts; F^+ transfer; Fluorination

1. Introduction

In connection with the development of a practical method for the preparation of 1,4-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts (**1**) [1], model reactions between 1:1 quinuclidine–Lewis acid (QLA) complexes (**2**) and elemental fluorine were investigated to establish suitable experimental procedures. This work provided two new *N*-fluoroquinuclidinium salts, namely the hexafluorophosphate **3b** and the fluorosulfonate **3c**, and hence the opportunity to compare the behaviour of these as electrophilic fluorinating agents with that of their known fluoride (**3d**), tetrafluoroborate (**3a**), and triflate (**3e**) analogues.

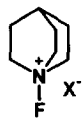


(1)



(2)

(a) L = BF_3
(b) L = PF_6
(c) L = SO_3



(3)

(a) $X^- = BF_4^-$
(b) $X^- = PF_6^-$
(c) $X^- = FSO_3^-$
(d) $X^- = F^-$
(e) $X^- = CF_3SO_3^-$

2. Results and discussion

2.1. Synthesis of *N*-fluoroquinuclidinium (NFQ^+) salts

The prototypical stable NFQ^+ salt *N*-fluoroquinuclidinium fluoride (**3d**) can be prepared in high yield (86%) by treating a cold (−72 °C) solution of quinuclidine in trichlorofluoromethane (CFC-11) with neat fluorine at low pressure [2]. Unfortunately, this user-friendly "F^+" transfer agent suffers from several drawbacks associated with the counter-anion, namely a marked hygroscopicity, lack of solubility in a sufficiently wide range of common solvents, and the possibility of encountering fluoride-initiated side reactions. Replacement of fluoride in NFQ^+F^- by triflate (TfO^-, trifluoromethanesulfonate) or tetrafluoroborate alleviates the solvent

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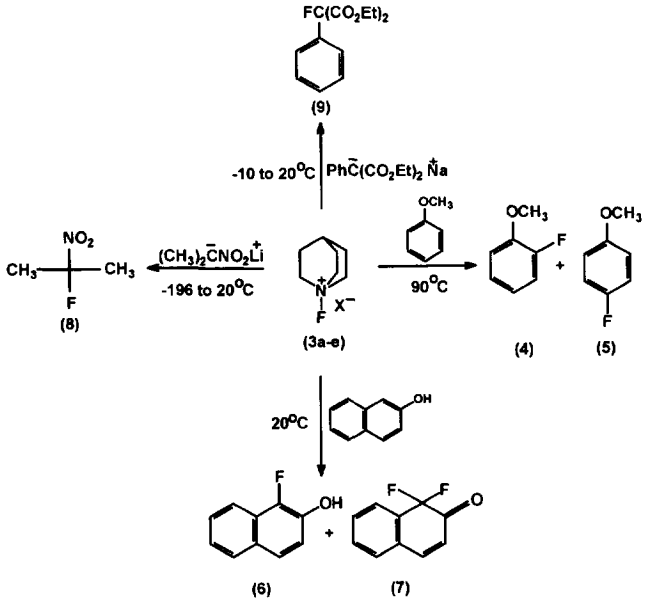

Fig. 1. Site-specific electrophilic fluorination with NFQ^+X^- salts.

problem, seemingly eliminates the tendency to absorb water from the air, and provides passive counter-ions (particularly TfO^-) [3].

Exchange of fluoride in NFQ^+F^- (**3d**) for $CF_3SO_3^-$ or BF_4^- can easily be achieved by adding an alkali–metal triflate or tetrafluoroborate to its solution in acetonitrile [3], or by treating quinuclidine in cold acetonitrile with elemental fluorine in the presence of the appropriate alkali–metal salt [3]. Fluorination of the known [4] 1:1 Lewis acid–Lewis base adduct quinuclidine–trifluoroborane (**2a**) in acetonitrile at ca. −35 °C with neat fluorine at low pressure (10–20 mmHg) in a closed system, or with a ca. 1:10 v/v fluorine–nitrogen blend in a flow system, has now been developed as an alternative procedure for the synthesis of $NFQ^+BF_4^-$. Good yields of purified product were achieved (closed system, 80%; flow, 71%), and the starting LA–LB adduct was prepared virtually quantitatively from quinuclidine and commercial boron trifluoride-etherate. The BF_3-based two-stage procedure $Q+F_2 \rightarrow NFQ^+F^- \rightarrow$ (with BF_3)$NFQ^+BF_4^-$ proved much more demanding experimentally (BF_3 boils at −99.9 °C [5]) and did not improve the yield.

Extension of the F_2–QLA reaction (flow system) to substrates **2b** and **2c** provided two new NFQ^+X^- reagents, namely *N*-fluoroquinuclidinium hexafluorophosphate (**3b**; 95%) yield and the analogous fluorosulfate (**3c**; 53%). In the case of $NFQ^+PF_6^-$, this method is neither as convenient nor as cheap on a laboratory scale as low-temperature flow fluorination (F_2–N_2 blend) of an equimolar mixture of quinuclidine and commercial sodium hexafluorophosphate dissolved in acetonitrile (yield 85%). No attempt was made to prepare $NFQ^+FSO_3^-$ from quinuclidine and fluorine in the presence of an alkali–metal fluorosulfonate because a commercial source of the last ingredient could not be located. The LA–LB starting material $Q \cdot SO_3$ was easily prepared by SO_3-transfer from commercial samples of pyridine-sulfur trioxide or (in better yield) dimethylformamide-sulfur trioxide.

2.2. Electrophilic fluorinations with NFQ^+X^- (3a–e)

Details of the site-specific electrophilic fluorinations carried out in a comparative set of experiments with NFQ^+X^- salts **3a–e** are summarised in Fig. 1 and Table 1. A previous study [3] included the noticeably hygroscopic (hence unsatisfactory) perfluoroalkanecarboxylates $NFQ^+R_FCO_2^-$ ($R_F = CF_3$, n-C_3F_7), but not, of course, the hexafluorophosphate **3b** or the fluorosulfate **3c**; and of the six substrates employed, only two (Me_2CLiNO_2 and 1-morpholinocyclohexene) were fluorinated using all five NFQ^+X^- salts examined [3]. The present study included two overtly carbanionic substrates used in the earlier work [$Me_2(O_2N)C^-\ Li^+$ and $Ph(EtO_2C)_2C^-\ Na^+$] and two new "masked" ones (C_6H_5OMe and 2-naphthol).

Table 1
Site-specific electrophilic fluorination with NFQ^+X^-

Substrate	Product	NFQ^+X^- Salt used and product yield (%) [a]				
		BF_4^- (3a)	PF_6^- (3b)	FSO_3^- (3c)	F^- (3d)	$CF_3SO_3^-$ (3e)
Methoxybenzene	2- and 4-fluoro-1-methoxybenzene (4+5) [b]	21	23	20	10	26
2-Hydroxynaphthalene	1-fluoro-2-hydroxynaphthalene (6) [c] + 1,1-difluoro-2-oxo-1-2-dihydronaphthalene (7) [c]	90	94	88	–	92
2-Nitropropan-2-yl-lithium	2-fluoro-2-nitropropane (8)	66	68	60	50	78
Diethyl sodio(phenyl) malonate	diethyl 2-fluoro-2-phenylmalonate (9)	56	56	52	55	58

[a] Yields estimated by GLC (uncalibrated) and ^{19}F NMR analysis of the crude product.
[b] 4:5 ratio ≈ 1:1 (see Table 2).
[c] 6:7 ratio ≈ 2:1.

The results provide no convincing evidence for the operation of a counter-anion effect, and reveal that there is not much to choose from the viewpoints of handling and product yield between the three best reagents, namely the triflate, the tetrafluoroborate and the hexafluorophosphate. However, the tetrafluoroborate is the most cost-effective; and of the three methods used to prepare this reagent [namely, (i) $Q+F_2 \rightarrow NFQ^+F^- \rightarrow$ (add $NaBF_4$) **3a**; (ii) $Q+F_2+NaBF_4$ (i.e. a one-pot reaction) $\rightarrow$ **3a**; (iii) $Q+BF_3 \rightarrow Q\cdot BF_3 \rightarrow$ (with F_2) **3a**], the one-pot reaction is the best laboratory procedure.

3. Experimental details

NMR spectra were recorded at 35 °C on Bruker AC-200 (^1H at 200 MHz; ext. TMS ref.; ^{19}F at 188.8 MHz, ext. TFA ref.; ^{11}B at 64.2 MHz, ext. BF_3 ref.; ^{31}P at 81.03 MHz, ext. H_3PO_4 ref.) and AC-300 [^1H at 300 MHz; ext. TMS ref.; ^{13}C at 75.5 MHz (broadband proton decoupling, D_2O lock, ext. TMS ref.)] spectrometers (chemical shifts to low field of refs. are designated positive). FAB mass spectra were obtained with a Kratos M550 instrument.

3.1. Preparation of quinuclidine–Lewis acid adducts

3.1.1. Quinuclidine–trifluoroborane (2a)

3.1.1.1. Using boron trifluoride-etherate

Commercial (Aldrich) boron trifluoride-etherate (6.4 g, 44.9 mmol) was added dropwise, under dry N_2, to a stirred solution of quinuclidine (5.0 g, 45.0 mmol) in dry diethyl ether (100 cm^3) contained in three-necked flask (ca. 250 cm^3) at 20 °C. A white precipitate formed immediately. The reaction mixture was stirred at room temperature for 1 h, then filtered; the solid obtained was washed with dry diethyl ether (3×20 cm^3) and dried in vacuo to give quinuclidine–trifluoroborane (**2a**) (8.0 g, 44.7 mmol, 99%) (Found: C, 46.6; H, 7.5; BF, 37.8; N, 7.9%. Calc. for $C_7H_{13}BF_3N$: C, 46.9; H, 7.3; BF, 37.9; N, 7.8%) as a white solid, m.p. 166 °C (lit.[4], 161–4 °C), δ_H (CD_3CN) 1.63 (m; 3,3,5,5,8,8-H), 1.92 (m; 4-H), 2.90 (m, 2,2,6,6,7,7-H), δ_C(CD_3CN) 19.409 (s; C-4), 22.967 (s; C-3,5,8), 46.278 (s, C-2,6,7), δ_F(CD_3CN) −78.80 (dd, J_{BF} 16.99 Hz; BF_3), δ_B(CD_3CN) −20.80 (s; BF_3) ppm, *m/z* (FAB) 112 {[*M*+1)-BF_3]$^+$, 100%}, 111[(*M*-BF_3)$^+$, 8%], 110 ($C_7H_{12}N^+$, 3%), 85 ($C_6H_{13}^+$, 17%), 84 ($C_6H_{12}^+$, 8%), 69 ($C_5H_9^+$, 4%), 56 ($C_4H_8^+$, 6%), 42 ($C_3H_6^+$, 17%).

3.1.1.2. Using boron trifluoride

Commercial (Fluorochem) boron trifluoride (1.0 g, 14.7 mmol) was condensed, in vacuo, into a cold (−196 °C) Pyrex Rotaflo tube (ca. 250 cm^3) containing quinuclidine (1.6 g 14.4 mmol) and dry acetonitrile (50 cm^3). The tube was sealed (PTFE-glass stopcock), placed in an explosion-proof cabinet and allowed to warm to room temperature before being shaken mechanically overnight. Volatile material (any unchanged BF_3 and some CH_3CN) was removed from the tube, in vacuo, then the solution remaining was evaporated (Rotavapor). The residual off-white solid was stirred with CH_3CN (10 cm^3) for 1 h at room temperature, then recovered by filtration and dried in vacuo to give pure quinuclidine–trifluoroborane (**2a**) (2.6 g, 14.5 mmol, 99%) with the correct spectroscopic properties.

3.1.2. Quinuclidine–pentafluorophosphorane (2b)

Commercial (Fluorochem) phosphorus pentafluoride (1.8 g, 14.3 mmol) was condensed, in vacuo, into a cold (−196 °C) Pyrex tube (ca. 250 cm^3) containing quinuclidine (1.6 g, 14.4 mmol) and dry acetonitrile (20 cm^3). The tube was sealed, placed in an explosion-proof cabinet and allowed to warm to room temperature before being shaken mechanically overnight (an excessive period). Volatile material (any unchanged PF_5 and some CH_3CN) was removed from the tube, in vacuo, then the solution remaining was evaporated (Rotavapor). The residual, yellowish solid was dissolved in dry acetonitrile (20 cm^3) and the solution obtained stirred for 1 h with decolorising charcoal, then filtered and the filtrate mixed with dry diethyl ether (15 cm^3 added dropwise, with stirring). The white solid which precipitated was recovered by filtration and dried in vacuo to give quinuclidine–pentafluorophosphorane (**2b**) (n.c.) (2.34 g, 9.87 mmol, 69%) (Found: C, 35.1; H, 5.2; N, 5.7%. Calc. for $C_7H_{13}F_5NP$: C, 35.4; H, 5.5; N, 5.9%), a white solid, m.p. 200–201 °C, δ_H (acetone-d_6) 2.10 (m; 3,3,5,5,8,8-H), 2.35 (m; 4-H), 3.60 (m; 2,2,6,6,7,7-H); δ_C (CD_3CN) 18.918 (s; C-4), 22.260 (s; C-3,5,8), 46.489 (s; C-2,6,7); δ_F(CD_3CN) +6.0 (d, J_{PF} 670.20 Hz; PF_5); δ_P(CD_3CN) −143.50 (m, J_{PF} 671.10 Hz, PF_5) ppm, *m/z* (FAB) 112 {[(*M*+1)-PF_5]$^+$, 100%}, 111 [(*M*-PF_5)$^+$, 8%], 107 (PF_4^+, 9%), 88 (PF_3^+, 7%), 84 ($C_6H_{12}^+$, 13%), 56 ($C_4H_8^+$, 1.5%), 42 ($C_3H_6^+$, 13%).

3.1.3. Quinuclidine–sulfur trioxide (2c)

Pyridine-sulphur trioxide (2.86 g, 18.0 mmol) in dry acetonitrile (20 cm^3) was added dropwise over 1 h to a stirred solution of quinuclidine (2.0 g, 18.0 mmol) in dry acetonitrile (30 cm^3). The reaction mixture was stirred overnight, mixed with dry diethyl ether (50 cm^3), and the white precipitate which appeared was recovered by filtration, washed with dry diethyl ether (3×20 cm^3), dried in vacuo and shown to be a 1:1 quinuclidine–sulphur trioxide complex (**2c**) (n.c.) (1.6 g, 8.4 mmol, 46.5%) (Found: C, 44.0; H, 7.0; N, 7.2%. Calc. for $C_7H_{13}NO_3S$: C, 44.0; H 6.8; N, 7.3%), a white hygroscopic solid, m.p. 266–228 °C [δ_H(CD_3CN) 2.10 (m; 3,3,5,5,8,8-H), 2.23 (m; 4-H), 3.64 (m; 2,2,6,6,7,7-H), δ_C (CD_3CN) 18.325 (s; C-4), 22.076 (s; C-3,5,8), 45.875 (s; C-2,6,7) ppm, *m/z* (FAB) 112 {[(*M*+1) −SO_3]$^+$ 100%}, 111 [(*M*−SO_3)$^+$, 12%)], 110 ($C_7H_{12}N^+$, 8.2%), 84 ($C_6H_{12}^+$, 14%), 82 ($C_6H_{10}^+$, 10%), 80 (SO_3^+, 8%), 64 (SO_2^+, 4%), 57 ($C_4H_9^+$, 2%), 42 ($C_3H_6^+$, 18%)].

The yield of complex **2c** increased to 76% when the reaction was repeated using commercial (Aldrich) dimethylformamide–sulfur trioxide as the source of SO_3.

3.2. Fluorination of quinuclidine–Lewis acid adducts

Two types of fluorination reactor were employed: closed and flow. The latter was identical with that used previously to fluorinate ureas in aqueous solution [6], except that no cold product traps were employed. The closed apparatus and associated method of usage have been described in detail previously in a paper [2] dealing with the direct fluorination of quinuclidine to give *N*-fluoroquinuclidinium fluoride (**3d**).

3.2.1. Quinuclidine–trifluoroborane (2a)

3.2.1.1. In a closed system

Using dry-box techniques, quinuclidine–trifluoromonoborane (1.5 g, 8.4 mmol) was dissolved in dry acetonitrile (20 cm^3) and the solution transferred to the fluorination reactor under nitrogen, to avoid contact with atmospheric moisture. Dry acetonitrile (180 cm^3) was then added to dilute the solution before it was cooled to −35 °C, stirred, and degassed by repeated evacuation to constant vapour pressure. Neat fluorine (0.35 g, 9.2 mmol) at 10–20 mmHg pressure was passed into the reactor during 3.5 h. The excess of fluorine was then pumped out via a KI scrubber before the reaction mixture was allowed to warm to room temperature and evaporated under reduced pressure (Rotavapor). The white solid residue was dissolved in the minimum quantity of dry acetone and then reprecipitated by adding dry ethyl acetate dropwise. The solid thus recovered was dried in vacuo and shown spectroscopically (NMR (^1H, ^{19}F, ^{13}C) and MS) to be *N*-fluoroquinuclidinium tetrafluoroborate (**3a**) (1.45 g, 6.68 mmol, 80%) (Found: C, 38.9; H, 5.7; N, 6.4%. Calc. for $C_7H_{13}BF_5N$: C, 38.7; H, 6.0; N, 6.5%), a white solid, m.p. 183–185 °C (lit.[3] 180–185 °C) [δ_H (CD_3CN) 2.30 (m; 4-H), 2.40 (m; 3,3,5,5,8,8-H), 4.51 (m; 2,2,6,6,7,7-H); δ_C (CD_3CN) 19.099 (d, J_{CF} 4.68 Hz; C-4), 27.378 (d, J_{CF} 4.08 Hz; C-3,5,8), 60.974 (d, J_{CF} 9.23 Hz; C-2,6,7); δ_F (CD_3CN) −72.50 (br.s; BF_4^-), +134.0 (br.s; N^+-F); δ_B (D_2O) −17.70 (s; BF_4^-) ppm; *m/z* (FAB) 217 (M^+, 2%), 130 [$(M-BF_4)^+$, 56%], 112 ($C_7H_{14}N^+$, 100%), 111 ($C_7H_{13}N^+$, 23%), 110 ($C_7H_{12}N^+$, 12%), 88 (HBF_4^+, 11%), 83 ($C_6H_{11}^+$, 13%), 82 ($C_6H_{10}^+$, 15%), 68 (BF_3^+, 35%), 42 ($C_3H_6^+$, 17%)].

3.2.1.2. In a flow system

Fluorine diluted with nitrogen (ca. 10% F_2 by volume) was bubbled slowly through a cold (−35 °C) vigorously stirred solution of quinuclidine–trifluoroborane (3.0 g, 16.8 mmol) in dry acetonitrile (100 cm^3) until the exit gas gave a strong positive test for fluorine (KI paper). Evaporation (Rotavapor) of the reaction mixture left a white solid residue, which was dissolved in the minimum quantity of AnalaR acetone, reprecipitated by adding dry ethyl acetate dropwise, recovered by filtration, dried in vacuo at room temperature, and shown by spectroscopic methods (^1H, ^{19}F, ^{13}C NMR, and MS) to be *N*-fluoroquinuclidinium tetrafluoroborate (**3a**) (2.6 g, 12.0 mmol, 71%).

"Expansion" of the BF_4^- signal (br.s) at −72.50 ppm in the ^{19}F NMR spectrum revealed that it comprised two peaks of relative intensities 1:4 at −72.36 and −72.44 ppm, respectively, corresponding to $^{10}BF_4^-$ and $^{11}BF_4^-$ (^{10}B:^{11}B = 20:80).

3.2.2. Quinuclidine–pentafluorophosphorane (2b)

3.2.2.1. In a flow system

Fluorine diluted with nitrogen (ca. 10% F_2 by volume) was bubbled slowly through a cold (−35 °C) vigorously stirred solution of quinuclidine–pentafluorophosphorane (2.0g, 8.4 mmol) in dry acetonitrile (100 cm^3) until the exit gas gave a strong positive test for fluorine (KI Paper). Evaporation of the reaction solution provided a white solid residue; this was dissolved in the minimum quantity of AnalaR acetone and reprecipitated by dropwise addition of dry diethyl ether to the solution, recovered by filtration, dried in vacuo at room temperature and shown by NMR spectroscopy (^1H, ^{19}F, ^{13}C) and mass spectrometry to be pure *N*-fluoroquinuclidinium hexafluorophosphate (**3b**; n.c.) (2.2 g, 8.0 mmol, 95%) (Found: C, 30.6; H, 4.7; F, 48.8; N, 5.2%. Calc. for $C_7H_{13}F_7NP$: C, 30.5; H, 4.7; F, 48.4; N, 5.1%), a white solid, m.p. 220 °C (turns brown at 235 °C in air) [δ_H (CD_3CN) 2.18 (m; 4-H), 2.30 (m; 3,3,5,5,8,8-H), 4.05 (q, $J^3_{HH} \approx J^3_{HF} \approx 7.5$ Hz; 2,2,6,6,7,7-H); δ_C (CD_3CN) 19.062 (d, J_{CF} 5.17 Hz; C-4), 27.349 (d, J_{CF} 4.08 Hz; C-3,5,8), 60.979 (d, J_{CF} 9.1 Hz; C-2,6,7); δ_F (CD_3CN) +5.63 (d, J_{PF} 709. Hz, PF_6^-), +135.1 (br.s; N^+-F); δ_P (D_2O) −143 (sept, J_{PF} 710.0 Hz; PF_6^-) ppm; *m/z* (FAB) 275 (M^+, 0.2%), 256 [$(M-F)^+$, 0.4%], 146 (HPF_6^+, 1%), 130 [$(M-PF_6^+)$, 36%], 126 (PF_5^+, 8%), 112 ($C_7H_{14}N^+$, 100%), 111 ($C_7H_{13}N^+$, 10%), 107 (PF_4^+, 22%), 88 (PF_3^+, 24%), 42 ($C_3H_6^+$, 18%)].

3.2.3. Quinuclidine–sulfur trioxide (2c)

A mixture of F_2 (0.2 g, 5.3 mmol) and N_2 (1.9 v/v) was passed at a rate of 130 cm^3 min^{-1} through a vigorously stirred solution of quinuclidine–sulfur trioxide complex (0.5 g, 2.6 mmol) in cold (−35 °C), dry acetonitrile (100 cm^3) umtil the exit gas gave a strong positive test for F_2 (KI paper). The reaction mixture was allowed to warm to room temperature, concentrated (to ca. 30 cm^3) by evaporation, then treated with dry diethyl ether (added dropwise) until no more a white solid precipitated. The solid was recovered by filtration, dried in vacuo, and shown to be impure *N*-fluoroquinuclidinium fluorosulfate (**3c**) (n.c) (0.32 g, 1.5 mmol, 53%) (Found: C, 34.5; H, 5.4; N, 5.7%. Calc. for $C_7H_{13}F_2NO_3S$: C, 36.7; H, 5.7; N, 6.1%), a hygroscopic white solid, m.p. 248 °C dec. [δ_H (CD_3CN) 2.20 (m; 4-H), 2.41 (m; 3,3,5,5,8,8-H), 4.02 (q, $J^3_{HH} \approx J^3_{HF} \approx 7.8$ Hz; 2,2,6,6,7,7-H); δ_C (CD_3CN)

19.036 (d, J_{CF} 5.08 Hz; C-4), 27.361 (d, J_{CF} 4.06 Hz; C-3,5,8), 60.939 (d, J_{CF} 8.98 Hz; C-2,6,7); δ_F (CD_3CN), −66.0 (s; FSO_3^-), +136.0 (br.s; N^+-F); *m/z*(FAB) 229 (M^+, 1%), 210 [$(M-F)^+$, 3%], 130 [$(M-FSO_3)^+$, 42%], 112 ($C_7H_{14}N^+$, 100%), 111 ($C_7H_{13}N^+$, 13%), 100 ($HFSO_3^+$, 8%), 83 ($C_6H_{11}^+$, 16%), 80 (SO_3^+, 21%), 69 ($C_5H_9^+$, 8.5%), 64(SO_2^+, 27%), 42 ($C_3H_6^+$, 31%)].

The purity of this product was determined titrimetrically (also by ^1H and ^{19}F NMR spectroscopy; the impurity was mainly unreacted starting material **2c**) by adding a known weight of the crude mixture (0.01 g) to an excess of KI (6.0 g) in 10% aqueous acetone and titrating the iodine liberated with aqueous 0.1 M sodium thiosulfate; the result corresponded to 91.6% pure N-F compound **3c**.

3.3. Synthesis of N-fluoroquinuclidinium hexafluorophosphate (3b) by direct fluorination of quinuclidine

3.3.1. In a closed system

Using the apparatus and techniques employed previously (Ref. [2]; see also Section 3.2.1.1) to prepare *N*-fluoroquinuclidinium fluoride in a Pyrex vacuum system, neat fluorine (0.7 g, 18.4 mmol) at 15–20 mmHg pressure was passed during 5 h into a degassed, vigorously stirred, cold (ca. −35 °C) solution of quinuclidine (2.0 g, 18.0 mmol) and sodium hexafluorophosphate (Fluorochem; 3.0, 17.9 mmol), in dry acetonitrile (50 cm^3). The reaction mixture was warmed to room temperature, filtered to remove the sodium fluoride which had precipitated, and then evaporated (Rotavapor) to dryness. The white solid thus isolated was purified by dissolution in AnalaR acetone (20 cm^3) and reprecipitated by dropwise addition of dry diethyl ether, recovered by filtration, finally dried in vacuo at 20 °C and shown by combustion and spectroscopic analysis to be *N*-fluoroquinuclidinium hexafluorophosphate (**3b**) (4.4 g, 16.0 mmol, 90%) (Found: C, 30.6; H, 4.7; F, 48.8; N, 5.2. Calc. for $C_7H_{13}F_7NP$ requires C, 30.5; H, 4.7; F, 48.4; N, 5.1%), m.p. 220 °C (decomp. at 235 °C) [δ_H (CD_3CN) 2.18 (m; 4-H), 2.30 (m; 3,3,5,5,8,8-H), 4.05 (q, $J^3_{HH} \approx J^3_{HF} \approx 7.5$ Hz; 2,2,6,6,7,7-H); δ_C (CD_3CN) 19.062 (d, $^4J_{CF}$ 5.17 Hz; C-4), 27.349 (d, $^3J_{CF}$ 4.08 Hz; C-3, 5,8), 60.979 (d, $^2J_{CF}$ 9.10 Hz; C-2, 6,7); δ_F (CD_3CN) 5.63 (d, J_{PF} 709 Hz; PF_6^-), +135.1 (broadened s; ^+NF) ppm, *m/z* (FAB) 275 (M^+, 0.2%), 130 [$(M-PF_6)^+$, 36%], 112 ($C_7H_{14}N^+$, 100%), 111 ($C_7H_{13}N^+$, 10%), 107 (PF_4^+, 22%, 88 (PF_3^+, 24%), 42 ($C_3H_6^+$, 18%)].

3.3.2. In a flow system

Fluorine (1.4 g, 37 mmol) diluted with nitrogen (ca. 10% F_2 by volume) was bubbled (130 cm^3 min^{-1}) through a vigorously-stirred cold (ca. −35 °C) dry acetonitrile (100 cm^3) containing dissolved quinuclidine (2.0 g, 18.0 mmol) and sodium hexafluorophosphate (3.03 g, 18.0 mmol). The reaction product was filtered (to remove NaF), then evaporated (Rotavapor); the crude *N*-fluoroquinuclidinium hexafluorophosphate (**3b**) thus recovered was purified by reprecipitation from AnalaR acetone with diethyl ether, dried in vacuo (yield = 4.20 g, 15.3 mmol, 85%) and found to have the same spectroscopic (IR, ^1H and ^{19}F NMR) parameters as the analytically-pure specimen described in Section 3.3.1.

3.4. Conversion of N-fluoroquinuclidinium fluoride (3d) to N-fluoroquinuclidiniumtetrafluoroborate (3a) using boron trifluoride

A cold (−196 °C) Rotaflo tube (ca. 250 cm^3) containing a de-gassed solution of *N*-fluoroquinuclidinium fluoride (2.0 g, 13.4 mmol) in dry acetonitrile (50 cm^3) was charged with boron trifluoride (0.92 g, 13.7 mmol), sealed, and placed in an explosion-proof cabinet to warm to room temperature. Its contents were then stirred (magnetically) overnight before volatile material (any unchanged BF_3 and some CH_3CN) was removed in vacuo. The remaining solution was evaporated (Rotavapor) to give an off-white solid residue. This was dissolved in the minimum quantity of AnalaR acetone, reprecipitated with dry ethyl acetate, recovered by filtration, dried in vacuo and shown by NMR spectroscopy technique to be *N*-fluoroquinuclidinium tetrafluoroborate (**3a**) (2.25 g, 10.37 mmol, 77%).

3.5. Site-specific electrophilic fluorinations with N-fluoroquinuclidinium salts (3a–e)

3.5.1. Methoxybenzene

A fluoroquinuclidinium salt was added to a solution of methoxybenzene in commercial acetonitrile (20 cm^3) in a Rotaflo tube (ca. 100 cm^3). The mixture was frozen (−196 °C), degassed, sealed in vacuo and allowed to warm to room temperature before being heated at 90 °C overnight (excessive period). The reaction mixture was allowed to cool to room temperature then diluted with diethyl ether (50 cm^3), extracted with water (3×30 cm^3) and finally dried ($MgSO_4$). Filtration of the mixture, followed by removal of the solvent under reduced pressure (Rotavapor), gave the crude product; this was examined by GLC [2 m silicone at 160 °C eluted with N_2; flame-ionization detector] and ^{19}F NMR spectroscopy and found to contain a mixture (ca. 1:1) of the known compounds 1-fluoro-2-methoxybenzene (**4**) and 1-fluoro-4-methoxybenzene (**5**) [δ_F ($CDCl_3$) −45.8 (m; 4-F), −57.7 (m; 2-F) ppm]. Details of the fluorination runs are given in Table 2.

3.5.2. 2-Hydroxynaphthalene

In each case, the *N*-fluoroquinuclidinium salt was added to a solution of 2-hydroxynaphthalene (Aldrich) in acetonitrile (10 cm^3) in a Rotaflo tube (ca 100 cm^3). The solution became yellow. The tube was cooled to −196 °C (liquid nitrogen), the contents degassed and the reactor sealed then allowed to warm to room temperature. After the reaction mixture had beeen stirred magnetically overnight, the product was extracted with dichloromethane (30 cm^3). The extract

Table 2
Fluorination of methoxybenzene with *N*-fluoroquinuclidinium salts

N-Fluoroquinuclidinium salt			Methoxybenzene		Product ratio [a]		Total yield [a]
No.	g	mmol	g	mmol	4	5	(%)
3a	0.50	2.30	0.25	2.30	52	48	21
3b	0.50	2.82	0.20	1.85	54	46	23
3c	0.10	0.44	0.05	0.46	50	50	20
3d	0.50	3.36	0.36	3.33	50	50	10
3e	0.50	1.79	0.20	1.85	60	40	26

[a] Yields and product ratios were estimated by GLC and ^{19}F NMR analysis (using the counter-anion signal as an internal standard).

was dried ($MgSO_4$), filtered and evaporated (Rotavapor) to give a ca. 2:1 mixture of the known compounds 1-fluoro-2-hydroxynaphthalene (**6**) [δ_F ($CDCl_3$) −73.60 (m) ppm] and 1,1-difluoro-2-oxo-1,2-dihydronaphthalene (**7**) [δ_F($CDCl_3$) −22.4 (m) ppm]. See Table 3 for details.

3.5.3. 2-Nitropropan-2-yl-lithium

Anhydrous methanol (30 cm^3) was condensed into a cold (−196 °C), evacuated, Pyrex Rotaflo tube (ca. 100 cm^3) containing a solid mixture of 2-nitropropan-2-yl-lithium and an *N*-fluoroquinuclidinium salt. The tube was degassed, sealed in vacuo, and allowed to warm to room temperature before the contents were stirred magnetically overnight. The reaction mixture was diluted with ether (50 cm^3), washed with aqueous 0.5 M oxalic acid (30 cm^3), 10% aqueous potassium bicarbonate (30 cm^3) and saturated sodium chloride solution (30 cm^3) (in that order) then dried ($MgSO_4$). The reaction product, recovered by removal of the solvent from the filtered reaction mixture (Rotavapor), was examined by GLC (2 m D.D.P. at 140 °C eluted with N_2; flame ionization detector) and NMR (^1H, ^{19}F) spectroscopy and found to contain the known compound 2-fluoro-2-nitropropane (**8**) [δ_F ($CDCl_3$) −33.7 (m; C-F) ppm]; see Table 4 for details.

3.5.4. Diethyl sodio(phenyl)malonate

Diethyl phenylmalonate was dissolved in anhydrous THF (15 cm^3) under N_2, and sodium hydride (ca. 10% excess) was added, in a three-necked round-bottomed flask (ca. 100 cm^3) equipped with a water-cooled reflux condenser and a calcium chloride tube. The mixture was then stirred until hydrogen evolution ceased (about 10 min), cooled to −10 °C (ice-salt bath) and then added to a stirred slurry of the *N*-fluoroquinuclidinium salt under examination in THF (20 cm^3) held at −10 °C (ice-salt bath) under N_2. The mixture thus prepared was stirred under N_2 until it reached room temperature before being diluted with diethyl ether (100 cm^3) and the whole washed with aqueous 0.5 M oxalic acid (30 cm^3), 10% aqueous potassium bicarbonate (30 cm^3) and saturated aqueous sodium chloride solution (30 cm^3), in that order, before it was dried ($MgSO_4$) and evaporated (Rotavapor) to remove the solvent. The residual yellow oil was shown by ^{19}F NMR spectroscopy to contain diethyl 2-fluoro-

Table 3
Fluorination of 2-hydroxynaphthalene with *N*-fluoroquinuclidinium salts

N-Fluoroquinuclidinium salt			2-Hydroxy-naphthalene		Total yield [a] (%) of (6+7) [b]
No.	g	mmol	g	mmol	
3c	0.20	0.87	0.13	0.90	88
3a	0.20	0.92	0.13	0.90	90
3b	0.20	0.73	0.11	0.76	94
3e	0.20	0.72	0.10	0.70	92

[a] Determined by ^{19}F NMR spectroscopy, using the counter-anion signal as an internal standard.
[b] **6**:**7** ratio ≈ 2:1.

Table 4
Fluorination of 2-nitropropan-2-yl-lithium with *N*-fluoroquinuclidinium salts

N-Fluoroquinuclidinium salt			2-Nitropropan-2-yl-lithium		Yield (%) [a] of **8**
No.	g	mmol	g	mmol	
3a	0.30	1.40	0.13	1.37	66
3b	0.30	1.01	0.10	1.05	68
3c	0.20	0.87	0.08	0.84	60
3d	0.30	2.01	0.19	2.00	50
3e	0.30	1.01	0.10	1.05	78

[a] Calculated using ^{19}F NMR spectroscopy, with C_6F_6 (0.01 g) as an internal standard.

Table 5
Fluorination of diethyl sodio(phenyl)malonate with *N*-fluoroquinuclidinium salts

N-Fluoroquinuclidinium salt			Diethyl phenylmalonate		Yield (%) [a] of **9**
No.	g	mmol	g	mmol	
3a	0.28	1.29	0.30	1.27	56
3b	0.35	1.27	0.30	1.27	56
3c	0.29	1.27	0.30	1.27	52
3d	0.19	1.28	0.30	1.27	55
3e	0.35	1.25	0.30	1.27	58

[a] Calculated using ^{19}F NMR spectroscopy, with C_6F_6 (0.01 g) as an internal standard.

2-phenylmalonate (**9**) [δ_F (neat) −81.60 (s) ppm]. Results are summarised in Table 5.

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